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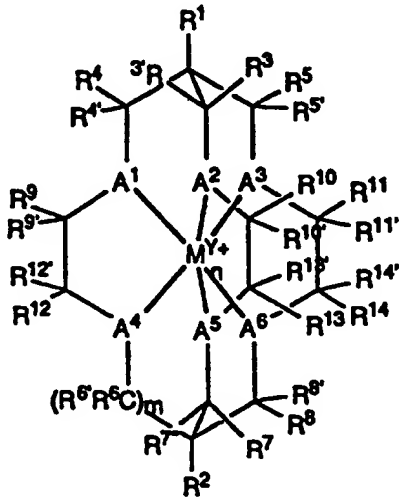
(54) Title: CAGE COMPOUNDS, PROCESSES FOR THEIR PREPARATION AND THEIR USE AS ANTIVIRAL AGENTS

(57) Abstract

A method of treatment and/or prophylaxis of a viral infection which comprises administration of an effective amount of a compound of formula (I), wherein M is a metal capable of forming hexacoordinate complexes; Y is an integer between 1 and 6; n is 0 or 1; m is 0 or 1; A^1 to A^6 are NH, N, O and S; R^1 to R^{14} and $R^{3'}$ to $R^{14'}$ have various values. Some of the compounds are novel.



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CAGE COMPOUNDS, PROCESSES FOR THEIR PREPARATION AND THEIR USE AS ANTIVIRAL AGENTS

The present invention relates to cage (Sarcophagine) compounds, processes for their preparation and their use in therapy, particularly for the treatment and/or prophylaxis of viral infections including Acquired Immune Deficiency Syndrome (hereinafter referred to as "AIDS"), Hepatitis B, Hepatitis C, Herpes and Cytomegalovirus (hereinafter referred to as "CMV").

Few antiviral drugs are currently in widespread clinical use because of the difficulty of inhibiting viruses while leaving the non-infected cells unimpaired. This is especially true of viruses within the families Retroviridae, Herpesviridae, Hepadnaviridae and Flaviviridae.

The causative agent for AIDS, the Human Immunodeficiency Virus, [also known as Human T-cell Lymphotropic Virus III (HLTV-III)] is a member of the family Retroviridae. This virus will be identified hereinafter as "HIV". Infection with HIV is associated with depletion of T4 lymphocytes, brain disease and several types of cancer including Kaposis sarcoma. Patients infected with the virus also have a high incidence of opportunistic infections and a significantly reduced life span. Another virus within the same family is the Human T-cell Lymphotropic Virus Type 1 (hereinafter referred to as "HLTV-1") the causative agent of Adult T-cell leukaemia, an infection with high mortality occurring in a distinctive geographical pattern.

All members of the family Retroviridae possess a unique enzyme, reverse transcriptase, which is necessary for their replication. As this enzyme is not normally present in uninfected cells, it is considered a target for antiviral drugs. Another virus utilizing reverse transcriptase during replication is the Hepatitis B Virus (hereinafter referred to as "HBV") which is a member of the family Hepadnaviridae. HBV causes widespread morbidity and mortality and is the main cause of primary hepatocellular carcinoma in individuals who are chronic carriers of the virus. It is also the cause of canine arthritis/encephalitis, feline arthritis and duck hepatitis.

The four forms of Herpesvirus responsible for human disease are Herpes Simplex virus (e.g., cold sores), Cytomegalovirus (e.g., salivary gland disease), Varicella-Zoster (e.g. chickenpox and shingles) and Epstein-Barr virus (e.g., infectious mononucleosis).

Treatment of Herpes Simplex virus (HSV) infections is recommended only in cases involving infection of slowly dividing host tissues, such as in keratoconjunctivitis. This is made necessary by the fact that idoxuridine (IUdR) and arabinoadenosine (ARA-A) can interfere with both viral DNA and host DNA, causing severe side effects. Severe systemic and neonatal HSV infections have been successfully treated with ARA-A, but extreme caution must be exercised in its use in order to prevent damage to blood-forming organs. Acyclovir is also approved for use against initial infections of herpes genitalis. The drug is used to control localized herpes simplex infections for both genital and labial herpes in patients whose natural defences are impaired and unable to control the spread of the infection. This drug reduces the length of time that live virions are present in the vesicles. This viral shedding in the lesion allows the virus to be transferred from one person to another through sexual contact, and the disease is highly contagious when sores are present. Another control attempt centers on the use of homologous vaccines made from attenuated HSV along with heterologous vaccines prepared from attenuated forms of viruses with cross-reacting antigens. For example, heterologous vaccination has been attempted with smallpox and polio vaccines. These have been given to patients with severe recurrent HSV infections such as cold sores, but they have benefited only a few individuals by reducing the recurrence rate. The value of this procedure has been questioned from several points: (i) the population already demonstrates a high HSV antibody titer; (ii) recurrent infections appear in the presence of high antibody titers; (iii) those with high antibody titers demonstrate the greatest recurrence rate; and (iv) HSV-II has suspected oncogenic properties that could possibly be demonstrated under certain circumstances.

Cytomegalic inclusion disease (hereinafter referred to as "CID") occurs most frequently in infants and is a viral disease of the salivary glands and other tissues. It is caused by the intrauterine (congenital) or postnatal transmission of CMV. Although rare, CID may also occur in adults receiving immunosuppressive therapy. Like other herpes viruses, CMV infections result in vesicular eruption of host tissues. The virus is not only found in the salivary glands but also the kidneys, liver, brain, lungs and eyes. Tissue destruction can be fatal or result in severe brain damage, blindness, deafness and heart defects. CMV is believed to be able to enter a latent period, as do other herpes viruses, resulting in a delay in the onset of symptoms of up to two years. At present, there is no treatment for this disease. A vaccine of attenuated CMV has been developed, but its value in preventing infection is questionable.

Flaviviruses are known to be the causative agents of a number of human diseases including the most important arthropod-borne viral afflictions of mankind - dengue, yellow fever, and Japanese encephalitis. In addition, eight flaviviruses cause disease in domestic or wild animals of economic importance. Yellow fever and dengue fever are widespread and well known as mosquito borne diseases of tropical countries. There are between 30 and 60 million flavivirus infections per year including one million Japanese encephalitis infections. The extent of Hepatitis C is not known with any degree of certainty because an infection can exist for many years without the patient being aware of the symptoms. Hepatitis C produces a much higher rate of chronic liver infection than Hepatitis B which is a recognised hazard in many countries. About 50% of patients develop chronic infections, compared with 5 to 10% of those infected with Hepatitis B. Chronic infection causes cirrhosis of the liver, impairs liver function and 20-30 years later causes liver failure. It has been estimated that the rate of infection approaches and may exceed 1% of the population in Australia. There is no proven cure or vaccine for Hepatitis C.

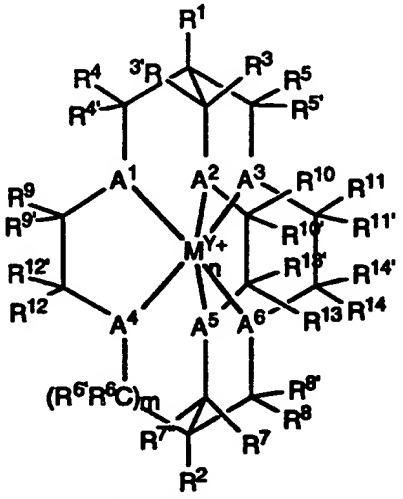
Effective vaccines are available for some Flaviviruses only, for example, yellow fever, Japanese encephalitis and tick-borne encephalitis. Treatment of dengue fever and Australian encephalitis relies on the patient's own immune defences; infections can be fatal. An antiviral drug to control infections with flaviviruses is thus highly desirable.

Cage compounds have been known for over 20 years (A. M. Sargeson, Pure and Applied Chemistry, Vol 58 page 1511(1986) and Chemistry in Australia, May 1992 page 176). Most of their applications stem from their redox chemistry and electron transfer properties. Their redox chemistry has led to their use as catalysts for the oxidation or reduction of organic substrates such as, for example, propylene to acrylic acid, ethylene to acetaldehyde. Their redox properties also led to their use as electron relays in the direct conversion of water to hydrogen using sunlight as energy source. In the biological field, cage ligands have been used to remove toxic metals, for example Cu and Fe, from the body by complexation followed by normal elimination of the stable complex. Because of the stability of the metal complexes in the body they have been suggested as carriers of isotopes or heavy metals for radionuclide or nmr imaging. It has also been reported that cage compounds with long alkyl chain tails, which are consequently surface-active, have the power to disrupt biological membranes and may be

useful as anthelmintics. The cage ligands or complexes have not previously been used as control agents for viral infections.

It has now been found that cage compounds of Formula 1 below are inhibitors of the replication of Retroviruses, Herpesviruses, Hepadnaviruses and Flaviviruses.

According to one aspect of the present invention there is provided a method for the treatment and/or prophylaxis of a viral infection which comprises administration of an effective amount of a compound of Formula 1:



Formula 1

wherein

M is a metal capable of forming hexacoordinate complexes;

Y is an integer between 1 and 6 inclusive;

n is 0 or 1;

m is 0 or 1;

A^1 to A^6 inclusive are metal coordinating groups which may be the same or different and are selected from NH, N, O and S;

R^1 and R^2 may be the same or different and are selected from hydrogen, halogen, nitro, cyano, optionally substituted alkyl, optionally substituted alkylene, optionally substituted aryl, hydroxy, optionally substituted alkoxy, optionally substituted alkyenyloxy, optionally substituted alkynyloxy, optionally substituted aryloxy, optionally substituted acyloxy,

optionally substituted amino, optionally substituted ammonium, optionally substituted cycloalkyl, optionally substituted acyl, optionally substituted saturated or unsaturated heterocyclyl, optionally substituted heteroaryl, carbamato, thiocarboxylato, amidino, alkoxycarbonyl, mercaptothiocarbonyl, alkoxythiocarbonyl, thiocarbamato, zinc halide and a sugar moiety; and

R^3 to R^{14} and $R^{3'}$ to $R^{14'}$ inclusive may be the same or different and are selected from hydrogen, halogen, optionally substituted alkyl, optionally substituted alkylene, hydroxy, optionally substituted alkoxy, optionally substituted alkyenyloxy, optionally substituted alkynyloxy, optionally substituted aryloxy, optionally substituted acyloxy, optionally substituted amino, optionally substituted ammonium, optionally substituted cycloalkyl, optionally substituted acyl, optionally substituted aryl, optionally substituted saturated or unsaturated heterocyclyl, optionally substituted heteroaryl, carbamato, thiocarboxylato, amidino, alkoxycarbonyl, mercaptothiocarbonyl, alkoxythiocarbonyl, thiocarbamato and a sugar moiety; or

one or more of the groups A^1 to A^6 may be linked to an adjoining carbon atom by a double bond with the absence of the corresponding to R^3 to R^{14} and $R^{3'}$ to $R^{14'}$ group;

salts thereof, pharmaceutically acceptable derivatives thereof, pro-drugs thereof, tautomers thereof and/or isomers thereof to a subject requiring said treatment and/or prophylaxis.

Throughout this specification unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

The term "viral infection" is used herein in its broadest sense and includes any infection caused by a Retrovirus such as HIV or HLTV-1; Herpesvirus such as CMV; Hepadnavirus such as HBV and duck hepatitis virus; or Flavivirus such as yellow fever virus, dengue virus and Japanese encephalitis virus. Such viral infections may include AIDS, Adult T-cell leukemia, cold sores, genital herpes, CID, chicken pox, shingles, infectious mononucleosis, Hepatitis B, Hepatitis C, non-A non-B Hepatitis, canine arthritis/encephaltis, feline arthritis, duck hepatitis, dengue fever, yellow fever and Japanese encephalitis.

The subject may be a human or an animal such as a domestic or wild animal, particularly an animal of economic importance.

An "effective amount" of the compound of Formula 1 is an amount sufficient to inhibit or reduce viral replication, generally by greater than 50% (as measured by viral DNA levels or reverse transcriptase activity).

The salts of the compound of Formula 1 are preferably pharmaceutically acceptable, but it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the present invention, since these are useful as intermediates in the preparation of pharmaceutically acceptable salts. Examples of pharmaceutically acceptable salts include salts of pharmaceutically acceptable cations such as sodium, potassium, lithium, calcium, magnesium, ammonium and alkylammonium; acid addition salts of pharmaceutically acceptable inorganic acids such as hydrochloric, orthophosphoric, sulphuric, phosphoric, nitric, carbonic, boric, sulfamic and hydrobromic acids; or salts of pharmaceutically acceptable organic acids such as acetic, propionic, butyric, tartaric, maleic, hydroxymaleic, fumaric, citric, lactic, mucic, gluconic, benzoic, succinic, oxalic, phenylacetic, methanesulphonic, trihalomethanesulphonic, toluenesulphonic, benzenesulphonic, salicyclic, sulphanilic, aspartic, glutamic, edetic, stearic, palmitic, oleic, lauric, pantothenic, tannic, ascorbic and valeric acids.

By "pharmaceutically acceptable derivative" is meant any pharmaceutically acceptable salt, hydrate or any other compound which, upon administration to the subject, is capable of providing (directly or indirectly) a compound of Formula 1 or an antivirally active metabolite or residue thereof.

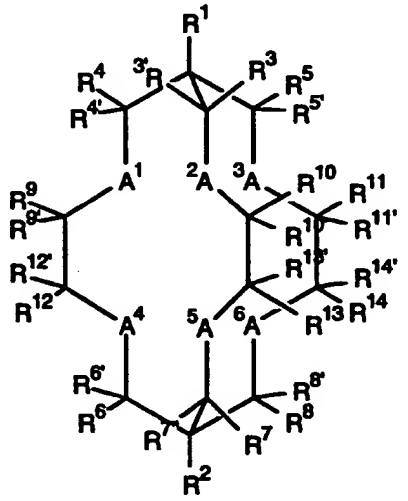
The term "pro-drug" is used herein in its broadest sense to include those compounds which are converted *in vivo* to compounds of Formula 1.

The term "tautomer" is used herein in its broadest sense to include compounds of Formula 1 which are capable of existing in a state of equilibrium between two isomeric forms. Such compounds may differ in the bond connecting two atoms or groups and the position of these atoms or groups in the compound,

The term "isomer" is used herein in its broadest sense and includes structural, geometric and stereo isomers. As the compound of Formula 1 may have one or more chiral centres, it is capable of existing in enantiomeric forms.

The compounds of the invention may be electrically neutral or be polycations with associated anions for electrical neutrality. Suitable associated anions include sulphate, tartrate, citrate, chloride, nitrate, nitrite, phosphate, perchlorate, halosulfonate or trihalomethylsulfonate.

When n is 0, the compounds of Formula 1 are metal free as shown in Formula 2 below. It will be appreciated that the compounds of Formula 2 may be converted to the compounds of Formula 1. The compounds of Formula 2 form another aspect of the present invention.

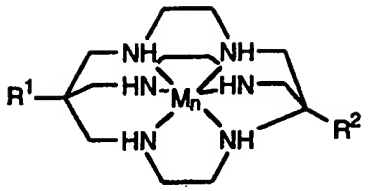


Formula 2

wherein

A^1 to A^6, R^1 to R^{14} and $R^{3'}$ to $R^{14'}$ are as defined above.

When m is 0, the compounds of Formula 1 include compounds of Formula 3 as shown below. The compounds of Formula 3 may be formed during the preparation of the compounds of Formula 1. The compounds of Formula 3 form a further aspect of the present invention.



Formula 3

wherein

R^1, R^2, M and n are as defined above.

The metal may be an alkali metal such as sodium or lithium; an alkaline earth metal such as magnesium; or a transition metal such as vanadium, titanium, chromium, manganese, iron, cobalt, nickel, copper, zinc, ruthenium, silver, cadmium, iridium, platinum, indium or mercury. Preferably, the metal is a Group 9 metal such as cobalt.

The term "halogen" denotes fluorine, chlorine, bromine or iodine, preferably chlorine, bromine or iodine.

The term "alkyl" used either alone or in compound words such as "optionally substituted alkyl" or "optionally substituted cycloalkyl" denotes straight chain, branched or cyclic alkyl, preferably C_{1-30} alkyl or cycloalkyl. Examples of straight chain and branched alkyl include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, amyl, isoamyl, sec-amyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2,-trimethylpropyl, 1,1,2-trimethylpropyl, heptyl, 5-methylhexyl, 1-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 1,2,3,-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, octyl, 6-methylheptyl, 1-methylheptyl, 1,1,3,3-tetramethylbutyl, nonyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-methyloctyl, 1-, 2-, 3-, 4- or 5-ethylheptyl, 1-, 2- or 3-propylhexyl, decyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- and 8-methylnonyl, 1-, 2-, 3-, 4-, 5- or 6-ethyloctyl, 1-, 2-, 3- or 4-propylheptyl, undecyl1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-methyldecyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-ethylnonyl, 1-, 2-, 3-, 4- or 5-propyloctyl, 1-, 2- or 3-butylheptyl, 1-pentylhexyl, dodecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-methylundecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-ethyldecyl, 1-, 2-, 3-, 4-, 5- or 6-propylnonyl, 1-,

2-, 3- or 4-butyloctyl, 1-2-pentylheptyl and the like. Examples of cyclic alkyl include mono- or polycyclic alkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and the like.

The term "alkenyl" used either alone or in compound words such as "alkenyloxy" denotes groups formed from straight chain, branched or cyclic alkenes including ethylenically mono-, di- or poly-unsaturated alkyl or cycloalkyl groups as defined above, preferably C_{2-20} alkenyl. Examples of alkenyl include vinyl, allyl, 1-methylvinyl, butenyl, iso-butenyl, 3-methyl-2-butenyl, 1-pentenyl, cyclopentenyl, 1-methyl-cyclopentenyl, 1-hexenyl, 3-hexenyl, cyclohexenyl, 1-heptenyl, 3-heptenyl, 1-octenyl, cyclooctenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 3-decenyl, 1,3-butadienyl, 1-4,pentadienyl, 1,3-cyclopentadienyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,3-cyclohexadienyl, 1,4-cyclohexaidenyl, 1,3-cycloheptadienyl, 1,3,5-cycloheptatrienyl and 1,3,5,7-cyclooctatetraenyl.

The term "alkoxy" used either alone or in compound words such as "optionally substituted alkoxy" denotes straight chain or branched alkoxy, preferably C_{1-30} alkoxy. Examples of alkoxy include methoxy, ethoxy, n-propyloxy, isopropyloxy and the different butoxy isomers.

The term "acyl" used either alone or in compound words such as "optionally substituted acyl" or "optionally substituted acyloxy" denotes carbamoyl, aliphatic acyl group and acyl group containing an aromatic ring, which is referred to as aromatic acyl or a heterocyclic ring which is referred to as heterocyclic acyl, preferably C_{1-30} acyl. Examples of acyl include carbamoyl; straight chain or branched alkanoyl such as formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl and icosanoyl; alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl and heptyloxycarbonyl; cycloalkylcarbonyl such as cyclopropylcarbonyl cyclobutylcarbonyl, cyclopentylcarbonyl and cyclohexylcarbonyl; alkylsulfonyl such as methylsulfonyl and ethylsulfonyl; alkoxysulfonyl such as methoxysulfonyl and ethoxysulfonyl; aroyl such as benzoyl, toluoyl and naphthoyl; aralkanoyl such as phenylalkanoyl (e.g. phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutyl, phenylpentanoyl and phenylhexanoyl) and naphthylalkanoyl (e.g. naphthylacetyl,

naphthylpropanoyl and naphthylbutanoyl); aralkenoyl such as phenylalkenoyl (e.g. phenylpropenoyl, phenylbutenoyl, phenylmethacrylyl, phenylpentenoyl and phenylhexenoyl and naphthylalkenoyl (e.g. naphthylpropenoyl, naphthylbutenoyl and naphthylpentenoyl); aralkoxycarbonyl such as phenylalkoxycarbonyl (e.g. benzyloxycarbonyl); aryloxycarbonyl such as phenoxycarbonyl and naphthyloxycarbonyl; aryloxyalkanoyl such as phenoxyacetyl and phenoxypropionyl; arylcarbamoyl such as phenylcarbamoyl; arylthiocarbamoyl such as phenylthiocarbamoyl; arylglyoxyloyl such as phenylglyoxyloyl and naphthylglyoxyloyl; arylsulfonyl such as phenylsulfonyl and naphthylsulfonyl; heterocycliccarbonyl; heterocyclicalkanoyl such as thienylacetyl, thienylpropanoyl, thienylbutanoyl, thienylpentanoyl, thienylhexanoyl, thiazolylacetyl, thiadiazolylacetyl and tetrazolylacetyl; heterocyclicalkenoyl such as heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl and heterocyclichexenoyl; and heterocyclicglyoxyloyl such as thiazolylglyoxyloyl and thienylglyoxyloyl.

The term "aryl" used either alone or in compound words such as "optionally substituted aryl", "optionally substituted aryloxy" or "optionally substituted heteroaryl" denotes single, polynuclear, conjugated and fused residues of aromatic hydrocarbons or aromatic heterocyclic ring systems. Examples of aryl include phenyl, biphenyl, terphenyl, quaterphenyl, phenoxyphenyl, naphthyl, tetrahydronaphthyl, anthracenyl, dihydroanthracenyl, benzanthracenyl, dibenzanthracenyl, phenanthrenyl, fluorenyl, pyrenyl, indenyl, azulenyl, chrysenyl, pyridyl, 4-phenylpyridyl, 3-phenylpyridyl, thienyl, furyl, pyrryl, pyrrolyl, furanyl, imadazolyl, pyrrolydinyl, pyridinyl, piperidinyl, indolyl, pyridazinyl, pyrazolyl, pyrazinyl, thiazolyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothienyl, purinyl, quinazolinyl, phenazinyl, acridinyl, benzoxazolyl, benzothiazolyl and the like. Preferably, the aromatic heterocylic ring system contains 1 to 4 heteratoms independently selected from N, O and S and containing up to 9 carbon atoms in the ring.

The term "heterocyclyl" used either alone or in compound words such as "optionally substituted saturated or unsaturated heterocyclyl" denotes monocyclic or polycyclic heterocyclyl groups containing at least one heteroatom atom selected from nitrogen, sulphur and oxygen. Suitable heterocyclyl groups include N-containing heterocyclic groups, such as, unsaturated 3 to 6 membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, for example, pyrrolyl,

pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl or tetrazolyl;

saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, such as, pyrrolidinyl, imidazolidinyl, piperidino or piperazinyl;

unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms, such as, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl or tetrazolopyridazinyl;

unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, such as, pyranyl or furyl;

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms, such as, thienyl;

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, oxazolyl, isoxazolyl or oxadiazolyl;

saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, morpholinyl;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, benzoxazolyl or benzoxadiazolyl;

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, thiazolyl or thiadiazolyl;

saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, thiazolidinyl; and

unsaturated condensed heterocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, benzothiazolyl or benzothiadiazolyl.

In this specification "optionally substituted" means that a group may or may not be further substituted with one or more groups selected from alkyl, alkenyl, alkynyl, aryl, halo, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, hydroxy, alkoxy, alkenyloxy, aryloxy, carboxy, benzyloxy haloalkoxy, haloalkenyloxy, haloaryloxy, nitro, nitroalkyl, nitroalkenyl, nitroalkynyl, nitroaryl, nitroheterocyclyl, azido, amino, alkylamino, alkenylamino, alkynylamino, arylamino, benzylamino, acylamino, acyl, alkenylacyl, alkynylacyl, arylacyl, acylamino, acyloxy, aldehydo, alkylsulphonyl, arylsulphonyl, alkylsulphonylamino, arylsulphonylamino, alkylsulphonyloxy, arylsulphonyloxy, heterocyclyl, heterocycloxy, heterocyclylamino,

haloheterocyclyl, alkylsulphenyl, arylsulphenyl, carboalkoxy, carboaryloxy, mercapto, alkylthio, arylthio and acylthio.

According to another aspect of the present invention there is provided the use of a compound of Formula 1 as defined above in the manufacture of a medicament for the treatment and/or prophylaxis of a viral infection.

The present invention also provides a compound of Formula 1 as defined above for use in the treatment and/or prophylaxis of a viral infection.

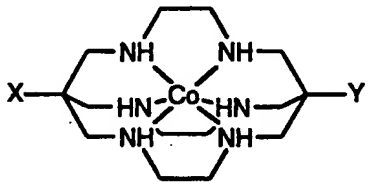
Compounds of Formula 1, 2 or 3 which fall within the ambit of the present invention include the compounds of Tables 1 to 6 and Figure 1 which follow. Amine groups in the compounds listed may be reversibly converted to ammonium under acidic conditions and the present invention includes both basic and protonated forms of such amine groups.

Some of the compounds of Formula 1 or 3 are novel *per se*. The novel compounds are shown in Tables 1 to 6 and Figure 1 which follow. Thus, in another aspect of the present invention there is provided Compound No. 1.3, 1.14, 1.16, 1.18, 1.20, 1.23, 1.24, 1.26, 1.28-1.45, 1.47-1.49, 1.51-1.56, 1.58, 1.60-1.62, 1.64, 1.81-1.87, 1.95-1.97 or 1.103-1.117 in Table 1, Compound No. 3.15 or 3.16 in Table 3, Compound No. 4.1-4.5 in Figure 1, Compound No. 5.2-5.12 in Table 4, Compound No. 6.1-6.9 in Table 5 or Compound No. 7.1-7.5 in Table 6.

In Tables 1 to 6, the following abbreviations are used:

Ac	=	Acetyl
Anthryl	=	Anthracenyl
en	=	ethylene diamine
Et	=	Ethyl
Me	=	Methyl
Pr	=	Propyl
p-TsNH	=	p-Tosylamino
PhthN	=	Phthalimido
Ph	=	Phenyl
Py	=	Pyridyl
Quin	=	Quinolinyl

Table 1



Compound number	X	Y	Compound number	X	Y
1.1	H	H	1.2	Me	H
1.3	Et	H	1.4	H	Cl
1.5	Me	Cl	1.6	H	Br
1.7	Me	Br	1.8	H	I
1.9	Me	I	1.10	Me	HO
1.11	Me	NO	1.12	H	NO_2
1.13	Me	NO_2	1.14	Et	NO_2
1.15	Me	NH_2	1.16	Et	NH_2
1.17	Me	HONH	1.18	Me	NC
1.19	Me	HOOC	1.20	Me	EtOOC
1.21	Me	AcOOC	1.22	Me	OCH
1.23	Et	$(HO)_2CH$	1.24	Me	PhCO
1.25	Me	Me_2N	1.26	Me	PhthN
1.27	Me	$PhCH_2NH$	1.28	Me	PhCH=N
1.29	Me	p-TsNH	1.30	Me	2-$HOPhCH_2NH$
1.31	Me	MeCONH	1.32	Me	2-HOPhCH=N
1.33	Me	4-$OCHPhCH_2N$	1.34	Me	4-OCHPhCH=N
1.35	Me	4-$HOCH_2Ph$-CH_2NH	1.36	Me	4-HOC(CN)Ph-CH_2NH
1.37	Me	4-$HOC(CONH_2)$-$PhCH_2NH$	1.38	Et	$Me_2NC_3H_6NHC(=NEt)NH$

Table 1 (Continued)

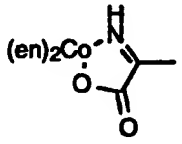
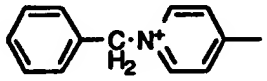
1.39	Me	9-anthrylCH$_2$NH	1.40	Me	9-anthrylCH$_2$NH-(CH$_2$)$_2$NH
1.41	Me	(C$_8$H$_{17}$)$_2$N(CH$_2$)$_2$NH	1.42	Me	(C$_8$H$_{17}$)$_2$N(CH$_2$)$_2$O
1.43	Me	C$_{12}$H$_{25}$O	1.44	Me	C$_6$H$_{13}$O
1.45	Me	Me$_2$CHO	1.46	Me	HOCH$_2$
1.47	Me	HOCOCH(NH$_2$)	1.48	Me	HOCOCH(OH)
1.49	Me	HOCOC(OH)$_2$	1.50	Me	Me
1.51	Me	Et	1.52	Et	Et
1.53	Me	Pr	1.54	Me	Bu
1.55	Me	C$_5$H$_{11}$	1.56	Me	C$_6$H$_{13}$
1.57	Me	C$_8$H$_{17}$	1.58	Me	C$_9$H$_{19}$
1.59	Me	C$_{10}$H$_{21}$	1.60	Et	C$_{12}$H$_{25}$
1.61	Me	C$_{15}$H$_{31}$	1.62	Me	C$_{18}$H$_{37}$
1.63	Me	Ph	1.64	Ph	Ph
1.65	H	Cl$_3$Zn	1.66	Me	Cl$_3$Zn
1.67	Me		1.68	Me	

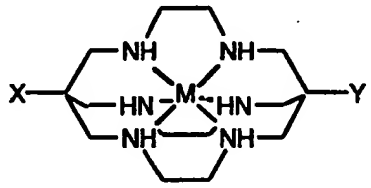
Table 1 (Continued)

1.69	Cl	Cl	1.70	Br	Br
1.71	HO	HO	1.72	NO_2	NO_2
1.73	NH_2	NH_2	1.74	MeNH	MeNH
1.75	Me_2N	Me_2N	1.76	Me_3N^+	Me_3N^+
1.77	PhthN	PhthN	1.78	p-TsNH	p-TsNH
1.79	NH_2	HONH	1 .80	HONH	HONH
1.81	$PhCH_2NH$	$PhCH_2NH$	1.82	PhCH=N	PhCH=N
1.83	MeCONH	MeCONH	1.84	HCONH	HCONH
1.85	OOCCH=CH=CO-NH	OOCCH=CHCO- NH	1.86	HOOC	HOOC
1.87	EtOOC	EtOOC	1.88	Cl	HO
1.89	Cl	NH_2	1.90	Cl	HONH
1.91	NO_2	Cl	1.92	NO_2	HO
1.93	NO_2	NH_2	1.94	NO_2	HONH
1.95	NH_2	$HNC_{10}H_{21}$	1.96	Me_3N^+	$Me_2N^+C_{10}H_{21}$
1.97	$HNC_{10}H_{21}$	$HNC_{10}H_{21}$	1.98	Me	4-Py
1.99	Me	N-Me-4-Py	1.100	Me	4-Quin
1.101	Me	N-Me-4-Quin	1.102	Me	N-CH_2Ph-4-Quin
1.103	Me	N-Me-Py-4-CH_2CH_2O	1.104	Me	^iPrO
1.105	Me	BuO	1.106	EtO	EtO
1.107	MeO	MeO	1.108	BuO	BuO

Table 1 (Continued)

1.109	$EtOCH_2CH_2O$	$EtOCH_2CH_2O$	1.110	Me	$EtOCH_2CH_2O$
1.111	NH_2	MeO	1.112	Bu	Bu
1.113	Et	Pr	1.114	Et	Bu
1.115	OH	$EtOCH_2CH_2O$	1.116	Me	MeO
1.117	Me	EtO			

Table 2

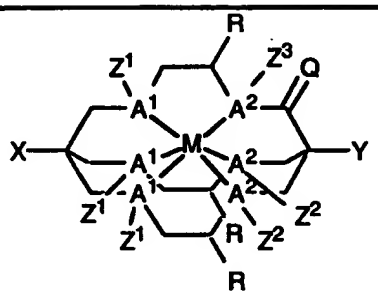


Compound number	M	X/Y	Compound Number	M	X/Y
2.1	Li^{I}	H	2.2	Mg^{II}	NH_2
2.3	Mg^{II}	H	2.4	V^{III}	H
2.5	V^{III}	H	2.6	V^{IV}	H(-2H)
2.7	V^{IV}	NH_2(-2H)	2.8	V^{IV}	H(-2H)
2.9	Ti^{III}	H	2.10	Cr^{II}	NH_2
2.11	Cr^{III}	H	2.12	Cr^{III}	NH_2
2.13	Cr^{III}	NO_2	2.14	Cr^{II}	$C_{10}H_{21}NH_2/NH_2$
2.15	Mn^{II}	H	2.16	Mn^{II}	NH_2
2.17	Mn^{III}	H	2.18	Fe^{II}	H
2.19	Fe^{II}	Me/H	2.20	Fe^{II}	NH_2
2.21	Fe^{III}	H	2.22	Fe^{III}	NH_2
2.23	Co^{II}	H	2.24	Co^{II}	NH_2
2.25	Ni^{II}	H	2.26	Ni^{II}	NH_2
2.27	Ni^{III}	H	2.28	Cu^{II}	H
2.29	Cu^{II}	NH_2	2.30	Zn^{II}	H
2.31	Zn^{II}	NH_2	2.32	Ga^{III}	H
2.33	Ru^{II}	H	2.34	Ru^{II}	H(cage imine)
2.35	Ru^{II}	H/Me	2.36	Ru^{III}	H
2.37	Ag^{II}	H	2.38	Ag^{II}	NH_2

Table 2 (Continued)

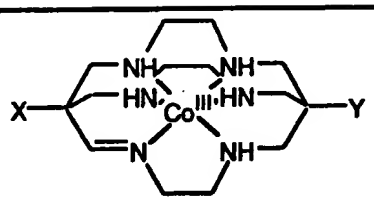
2.39	Rh^{III}	H	2.40	Rh^{III}	NO_2
2.41	Rh^{III}	NH_2	2.42	Rh^{III}	NO_2/NH_2
2.43	Rh^{III}	NH_2/Me	2.44	Cd^{II}	H
2.45	Cd^{II}	NH_2	2.46	Ir^{III}	H
2.47	Ir^{III}	NO_2	2.48	Ir^{III}	NH_2
2.49	Pt^{IV}	H	2.50	Pt^{IV}	NO_2
2.51	Pt^{IV}	$NO_2(-H^+)$	2.52	Pt^{IV}	NHOH
2.53	In^{III}	H	2.54	Hg^{II}	H
2.55	Hg^{II}	NH_2			

Table 3



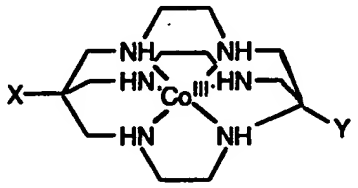
Compound number	X	Y	A^1	A^2	Z^1	Z^2	Z^3	R	Q	M
3.1	H	H	N	N	H	H	H	H	H_2	-
3.2	Me	H	N	N	H	H	H	H	H_2	-
3.3	NH_2	NH_2	N	N	H	H	H	H	H_2	-
3.4	Me	COO^-	N	N	H	H	-	H	O	Co
3.5	H	H	N	N	Me	Me	Me	H	H_2	-
3.6	NH_2	NH_2	N	N	H	H	H	Me	H_2	-
3.7	NH_2	NH_2	N	N	H	H	H	Me	H_2	Co
3.8	Me	Me	S	S	-	-	-	H	H_2	Co
3.9	NO_2	Me	N	S	H	-	-	H	H_2	Co
3.10	NH_2	Me	N	S	H	-	-	H	H_2	Co
3.11	NH_2	Me	N	S	H	-	-	H	H_2	-
3.12	Cl	Me	N	S	H	-	-	H	H_2	Co
3.13	OH	Me	N	S	H	-	-	H	H_2	Co
3.14	H	Me	N	S	H	-	-	H	H_2	Co
3.15	Me	Me	N	S	H	-	-	H	H_2	Co
3.16	Me	Me	N	S	H	-	-	H	H_2	-

Table 4



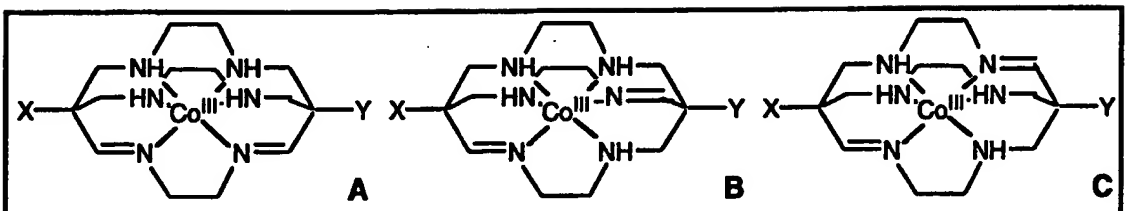
Compound number	X	Y	Compound number	X	Y
5.1	H	Me	5.2	H	Et
5.3	H	Pr	5.4	H	Ph
5.5	Et	Et	5.6	$C_{12}H_{25}$	Et
5.7	Me_2CH	Me	5.8	Et	Me
5.9	Pr	Me	5.10	Bu	Me
5.11	Pr	Et	5.12	Bu	Et

Table 5



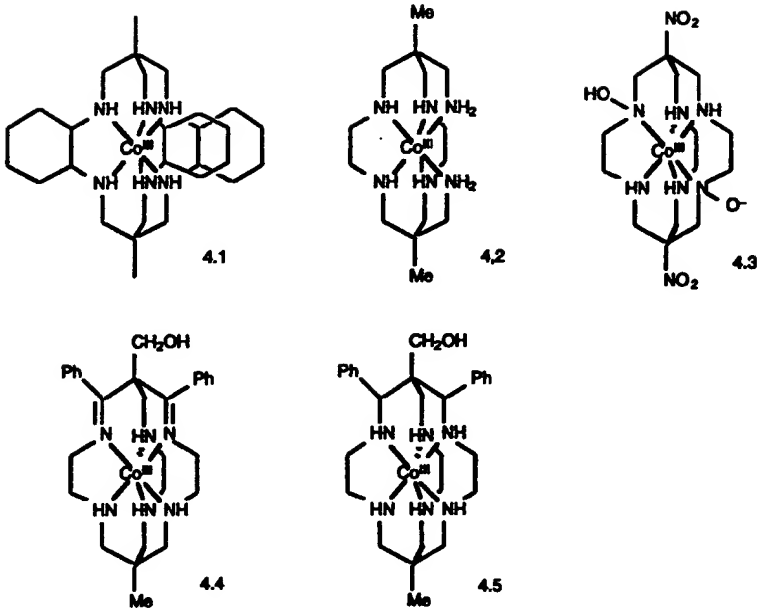
Compound number	X	Y	Compound number	X	Y
6.1	MeO	$MeOCH_2$	6.2	EtO	$EtOCH_2$
6.3	BuO	$BuOCH_2$	6.4	$EtOCH_2CH_2O$	$EtOCH_2CH_2OCH_2$
6.5	OH	$EtOCH_2CH_2OCH_2$	6.6	NH_2	$MeOCH_2$
6.7	Me	$EtOCH_2$	6.8	Me	$BuOCH_2$
6.9	Me	$EtOCH_2CH_2OCH_2$	6.10	Cl	$ClCH_2$

Table 6



Compound number	X	Y	Compound number	X	Y
7.1A	Me	Me	7.2A	Et	Et
7.1B	Me	Me	7.2B	Et	Et
7.1C	Me	Me	7.2C	Et	Et
7.3A	Pr	Pr	7.4A	Bu	Bu
7.3B	Pr	Pr	7.4B	Bu	Bu
7.3C	Pr	Pr	7.4C	Bu	Bu
7.5A	Ph	Ph			
7.5B	Ph	Ph			
7.5C	Ph	Ph			

Figure 1



The present invention also extends to a pharmaceutical or veterinary composition for the treatment and/or prophylaxis of a viral infection which comprises a compound of Formula 1, 2 or 3 as defined above in association with a pharmaceutically or veterinarily acceptable carrier, diluent, adjuvant and/or excipient.

The compounds of the invention may be advantageously used in therapy in combination with other medicaments or in conjunction with other immune modulating therapy including bone marrow or lymphocyte transplants or medications such as levamisol or thymosin which would increase lymphocyte numbers and/or function as appropriate. Hence a preferred method in accordance with the present invention utilises the compound of Formula 1, 2 or 3 in conjunction with another medicament.

The compound of Formula 1, 2 or 3 hereinafter referred to as the "active ingredient" may be administered for therapy by any suitable route, including oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous and intradermal). Preferably, administration will be by the oral route, however it will be appreciated that the preferred route will vary with the condition and age of the subject and the chosen active ingredient.

The compositions of the present invention comprise at least one compound of Formula 1, 2 or 3, together with one or more pharmaceutically acceptable carriers, diluents adjuvants and/or excipients and optionally other antiviral or therapeutic agents. Each carrier, diluent, adjuvant and/or excipient must be pharmaceutically "acceptable" in the sense of being compatible with the other ingredients of the composition and not injurious to the subject. Compositions include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The compositions may conveniently be presented in unit dosage form and may be prepared by methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers, diluents, ajduvants and/or excipients or finely divided solid carriers or both, and then if necessary shaping the product.

Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g inert diluent, preservative disintegrant (e.g. sodium starch glycollate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Compositions suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavoured basis, usually sucrose and acacia or tragacanth gum; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia gum; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Compositions for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Compositions suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the composition isotonic with the blood of the intended subject; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage compositions are those containing a daily dose or unit, daily sub-dose, as hereinabove described, or an appropriate fraction thereof, of an active ingredient.

The compounds of Formula 1, 2 or 3 may also be presented for use in the form of veterinary compositions, which may be prepared, for example, by methods that are conventional in the art. Examples of such veterinary compositions include those adapted for:

(a) oral administration, external application, for example drenches (e.g. aqueous or non-aqueous solutions or suspensions); tablets or boluses; powders, granules or pellets for admixture with feed stuffs; pastes for application to the tongue;

(b) parenteral administration for example by subcutaneous, intramuscular or intravenous injection, e.g. as a sterile solution or suspension; or (when appropriate) by intramammary injection where a suspension or solution is introduced into the udder via the teat;

(c) topical application, e.g. as a cream, ointment or spray applied to the skin; or

(d) intravaginally, e.g. as a pessary, cream or foam.

It should be understood that in addition to the ingredients particularly mentioned above, the compositions of this invention may include other agents conventional in the art having regard to the type of composition in question, for example, those suitable for oral administration may include such further agents as binders, sweeteners, thickeners, flavouring agents, disintegrating agents, coating agents, preservatives, lubricants and/or time delay agents.

Suitable sweeteners include sucrose, lactose, glucose, aspartame or saccharin. Suitable disintegrating agents include corn starch, methylcellulose, polyvinylpyrrolidone, xanthan gum, bentonite, alginic acid or agar. Suitable flavouring agents include peppermint oil, oil of wintergreen, cherry, orange or raspberry flavouring. Suitable coating agents include polymers or copolymers of acrylic acid and/or methacrylic acid and/or their esters, waxes, fatty alcohols, zein, shellac or gluten. Suitable preservatives include sodium benzoate, vitamin E, alpha-tocopherol, ascorbic acid, methyl paraben, propyl paraben or sodium bisulphite. Suitable lubricants include magnesium stearate, steric acid, sodium oleate, sodium chloride or talc. Suitable time delay agents include glyceryl monostearate or glyceryl distearate.

The compounds of Formula 1, 2 or 3 may be prepared by processes described in the scientific literature. In particular, the metal atom in the compounds of Formula 1 or 3 may be incorporated or exchanged by the processes described in P. Comba, L. M. Engelhardt, J. M. Harrowfield, G. A. Lawrance, L. L. Martin, A. M. Sargeson and A. H. White, J. Chem. Soc. Chem. Commun. 1985, 174; P. Bernhard and A. M. Sargeson, J. Chem. Soc. Chem. Commun. 1985, 1516; I. J. Clark. I. I. Creaser, L. M. Engelhardt, J. M. Harrowfield, E. R. Krausz, G. M. Moran, A. M. Sargeson; and A. H. White, Aust. J. Chem., 1993, 46, 111-126.

The compounds of Formula 2 may be prepared by processes described in L. L. Martin, Ph. D. Thesis, Australian National University, 1986, pp 229-233. D. J. Bull, Ph. D. Thesis, Australian National University, 1991, pp 41; Bottomley, G. A.; Clark, I. A.; Creaser, I. I.; Engelhardt, L. M.; Geue, R. J.; Hagen, K. S.; Harrowfield, J. M.; Lawrance, G. A.; Lay, P. A.; Sargeson, A. M.; See, A. J.; Skelton, B. W.; White, A. H.; and Wilner, F. R., *Aust. J. Chem.*, 1994, *47*, 143.

Compounds wherein $R^1 = R^2$ can be prepared by processes described in R. J. Geue, T. W. Hambley, J. M. Harrowfield, A. M. Sargeson and M. R. Snow, J. Amer. Chem. Soc. 1984, 106, 5478-5488.

Compounds wherein one of R^1 or R^2 is lower alkyl can be prepared by the processes described in B. Korybut-Daskiewicz, R. M. Hartshorn and A. M. Sargeson, J. Chem. Soc. Chem. Commun. 1989, 1375 and A. Höhn, R. J. Geue and A. M. Sargeson, J. Chem. Soc. Chem. Commun. 1990, 1473-1475.

Compounds wherein the A groups are a mixture of N and S can be made by processes described in Lay, P. A.; Lydon, J.; Mau, A. W.-H.; Osvath, P.; Sargeson, A. M.; and Sasse, W. H. F., *Aust. J. Chem.*, 1993, 46, 641.

Compounds wherein the A groups are S can be made by the methods disclosed in P. Osvath, A. M. Sargeson, B. W. Skelton and A. H. White, J. Chem. Soc. Chem. Commun.,1991, 1036-1038.

The present invention further provides a process for the preparation of a compound of Formula 1 as defined above wherein n is 1 and A^1 to A^6 inclusive are N or NH which comprises the steps of:

(a) reacting a metal complex having at least three terminal primary amino groups with formaldehyde, a base and a nucleophile optionally containing a functional group which may react with any co-ordinated amine which may also be present on the metal complex leading to encapsulation and the formation of a cage molecule; and

(b) optionally modifying the cage molecule.

The process of the present invention results in the formation of "end-caps", that is, the groups to which R^1 or R^2 are attached. The end-caps may also include the R^1 or R^2 groups. The end-capping process is based on a series of reactions which take place at terminal amine groups of ligands co-ordinated to the metal atom. A metal complex having ligands with terminal primary amino groups is treated with formaldehyde and base. It is believed that deprotonation of one amine group is followed by condensation with formaldehyde to give a co-ordinated carbinolamine, which eliminates water to give an imine. The imine may then be attacked by a nucleophile, such as, an amine or a carbanion leading to a coupled species. Under the conditions of the reaction, this mechanism may occur one or more times to give the cage molecule.

The nucleophilic species may contain one or more functional groups, such as, an aldehyde, carboxylate or nitrile. These functional groups may also attack the co-ordinated amines and lead to ring closure, in which case fewer than three units of formaldehyde are required to form the cap. Depending on the nature of the metal complex, the capping process can take place on one or both ends of the molecule to give the cage. This sequence of the coupling reactions and the nucleophilic attack may vary, but the overall result is the formation of the caps, leading to encapsulation of the metal.

The process may be performed in any suitable solvent, for example, water or acetonitrile. The order of addition of the reagents can also be varied. It is not necessary for the reagents to be fully dissolved for the reaction to occur. Either aqueous formaldehyde or paraformaldehyde may be the source of formaldehyde. A variety of different bases, such as, inorganic hydroxides and carbonates or tertiary amines may be used in the process.

Once the cage has been formed it may be modified, for example, by attaching functional groups or by reduction.

The invention will now be described with reference to the following non-limiting Examples. These Examples are not intended to limit the scope of the invention in any way.

The term "active ingredient" as used in Examples 9 to 11 means a compound of Formula 1, 2 or 3.

In the Examples, ^{1}H and proton-decoupled ^{13}C n.m.r. spectra were recorded with a Varian Gemini 300 MHz Fourier Transform n.m.r. spectrometer, using 1,4-dioxane as internal reference for solutions of metal complexes in D_2O. The signals of dioxane are taken as δ = 3.74 ppm for ^{1}H n.m.r. and δ = 67.39 ppm for ^{13}C n.m.r. spectra. ^{13}C peak multiplicities were assigned by the use of DEPT and APT techniques as appropriate.

EXAMPLE 1 - *"End - Capping" Reaction*

(a) Procedure for Preparation of [Co(Me, Etim-sar)]Cl3 (Compound 5.8)

[Co(sen)].Cl_3 (3.42 g, 8.3 mmol) (sen = 5-(4-amino-2-azabutyl)-5-methyl-3,7-diazanonane-1,9-diamine) and $NaClO_4.H_2O$ (10g) were added to acetonitrile (50mL) and the solution was stirred for 15 minutes, during which time some of the complex dissolved. To the stirred suspension was added paraformaldehyde (0.55 g, 18.2 mmol) and (freshly distilled) n-butanal (1.5 mL, 16.6 mmol). After the mixture was stirred for a further 5 minutes, triethylamine (3.5 mL, 25 mmoles) was added. The mixture rapidly turned dark brown. After stirring for 30 minutes, the reaction mixture was quenched with excess glacial acetic acid, diluted with 0.5 M HCl (500 mL), and loaded onto a column of Dowex 50W-X2 cation exchange resin. The column was washed with water, then 1M HCl and the adsorbed complexes were removed as a single band with 2M HCl. Some material was removed from the column with concentrated HCl/Absolute Ethanol (1:1), but this was shown by n.m.r. to contain none of the desired product. The (2 M HCl) eluate was taken to dryness, diluted to 500 mL with water, loaded onto a column of SP-Sephadex C-25 (35 x 4 cm) and eluted with K_2SO_4 (0.1 M). The leading half of the single yellow band that was eluted contained the desired product. This material was desalted by treatment with Dowex-HCl, and rechromatographed on SP-Sephadex C-25, using Na3citrate (0.05 M) as eluant. The single yellow band was collected in four fractions and the second and third of these contained only the desired product. (The first and fourth fractions were largely the target molecule as well, but were not pure).

The product was desalted on Dowex, stripped to dryness, and dissolved in the minimum amount of boiling methanol. Upon cooling to 0°C, the product was obtained as a well-crystallised material.

^{13}C n.m.r. δ(75MHz,D_2O): 8.6 ($\underline{C}H_3CH_2$); 21.0 ($\underline{C}H_3C_q$); 26.7 ($CH_3\underline{C}H_2$), 41.7 ($CH_3\underline{C}_q$); 53.0 ($\underline{C}_qC{=}N$); 51.9, 52.1, 52.6, 53.3, 54.9, 55.0, 55.3, 56.0, 56.9, 59.0 (NCH_2); 61.8 (C=N–$\underline{C}H_2$); 187.5 ($\underline{C}{=}N$).

(b) Procedure for Preparation of [Co(Me,Et-sar)]Cl3 (Compound 1.51)

[Co(sen)].Cl_3 (0.86 g, 2.1 mmol) and $NaClO_4.H_2O$ (2.5g) were added to acetonitrile (15 mL) and the solution was stirred for 15 minutes, during which time some of the complex dissolved. To the stirred suspension was added paraformaldehyde (0.14 g, 4.55 mmol) and (freshly distilled) n-butanal (0.375 mL, 4.2 mmol). After the mixture was stirred for a further 5 minutes, triethylamine (0.9 mL, 6.3 mmoles) was added. The mixture rapidly turned dark brown. After stirring for 30 minutes, the reaction mixture was quenched with excess glacial acetic acid, diluted with 0.5 M HCl (500 mL) and loaded onto a column of Dowex 50W-X2 cation exchange resin. The column was washed with water, then 1M HCl and the adsorbed complexes were removed as a single band with 2M HCl. The eluate was taken to dryness, and the crude product was dissolved in water (15 mL). $NaHCO_3$ (0.90 g) was added, followed immediately by a solution containing $NaBH_4$ (0.079 g) and Na_2CO_3 (1.0g) in water (10 mL), and the solution was stirred for 30 minutes. The reaction mixture was quenched with excess 1M HCl (caution, frothing) and air was bubbled through the solution for 15 minutes. The solution was loaded onto a column of Dowex 50W-X2 cation exchange resin, washed with water, then 1M HCl and the desired complex was removed with 2M HCl. The column was then washed with 6M HCl to remove some polymeric impurity. The (2M) fraction which contained the metal complexes was stripped to dryness, and the crude product was taken up in the minimum volume of hot water and diluted with an equal volume of 2-propanol, giving the desired product as a well-crystallised material.

^{13}C n.m.r. δ(75MHz,D_2O): 7.7 ($\underline{C}H_3CH_2$); 20.4 ($\underline{C}H_3C_q$); 28.1 ($CH_3\underline{C}H_2$); 43.0 ($\underline{C}H_3C_q$); 46.2 ($CH_3CH_2\underline{C}_q$); 54.4, 55.7, 55.9 (~double intensity) (NCH_2).

EXAMPLE 2 - *"Double End - Capping" Reaction*

(a) Procedure for the Preparation of the Three Isomers of [Co(Et2im2-sar)]Cl3 (Compound 7.2)

$[Co(en)_3]Cl_3.H_2O$ (3.03 g, 8.3 mmol) and $NaClO_4.H_2O$ (10g) were added to acetonitrile (50mL) and the solution was stirred for 15 minutes, during which time some of the complex dissolved. To the stirred suspension was added paraformaldehyde (1.25 g, 42 mmol) and (freshly distilled) n-butanal (3.0 mL, 33 mmol). After the mixture was stirred for a further 5 minutes, triethylamine (4 mL, 29 mmoles) was added. The mixture rapidly turned purple-brown. After stirring for 30 minutes, the reaction mixture was quenched with glacial acetic acid (20 mL), diluted with 0.05 M HCl (750 mL) and loaded onto a column of Dowex 50W-X2 cation exchange resin. The column was washed with successively with water, 0.5 M HCl and 1M HCl and the adsorbed complexes were removed as a single band with 2 - 4 M HCl. Some material was removed from the column with concentrated HCl/Absolute Ethanol (1:1), but this was shown by n.m.r. to contain none of the desired product. The (2 - 4 M HCl) eluate was taken to dryness, diluted to 500 mL with water, loaded onto a column of SP-Sephadex C-25 (35 x 4 cm) and eluted with K_2SO_4 (0.1 M adjusted to pH 4 with HCl). An initial fast-moving green band was discarded. This was followed successively by a red band (R1), a yellow band (Y1), a pale yellow band (Y2), a yellow band (Y3), a pale yellow band (Y4) and a final yellow band (Y5). Each band was desalted on Dowex, using HCl and taken to dryness. Bands R1, Y2 and Y4 were minor fractions and their n.m.r. spectra indicated that they each contained a number of different compounds, whose separation and characterisation was not pursued further. The n.m.r. spectra of Y1, Y3 and Y5 indicated that these correspond to the three possible isomers of $[Co(Et_2im_2\text{-sar})]Cl_3$.

Y1: ^{13}C N.M.R. δ(75MHz,D_2O): 8.4 ($\underline{C}H_3CH_2$); 26.3 ($CH_3\underline{C}H_2$), 53.1 ($\underline{C}_qC{=}N$); 53.0, 54.4, 55.8, 56.3 (NCH_2); 62.1 ($C{=}N{-}\underline{C}H_2$); 185.7 ($\underline{C}{=}N$).

Y2: ^{13}C N.M.R. δ(75MHz,D_2O): 8.6 ($\underline{C}H_3CH_2$); 26.4 ($CH_3\underline{C}H_2$), 53.7 ($\underline{C}_qC{=}N$); 51.8,51.9, 54.4, 56.0 (NCH_2); 65.3 ($C{=}N{-}\underline{C}H_2$); 187.2 ($\underline{C}{=}N$).

Y3: ^{13}C N.M.R. δ(75MHz,D_2O): 8.3 ($\underline{C}H_3CH_2$); 26.7 ($CH_3\underline{C}H_2$), 52.7 ($\underline{C}_qC{=}N$); 50.6, 51.5, 52.6, 53.0 (NCH_2); 62.4 ($C{=}N{-}\underline{C}H_2$); 187.7 ($\underline{C}{=}N$).

(b) Procedure for Preparation of [Co(Et2-sar)]Cl3 (Compound 1.52) *by Double Capping of [Co(en)3]Cl3.H2O Followed by Reduction*

[Co(en)3]Cl3.H2O (0.76 g, 2.1 mmol) and $NaClO_4.H_2O$ (2.5 g) were added to acetonitrile (15 mL) and the solution was stirred for 15 minutes, during which time some of the complex dissolved. To the stirred suspension was added paraformaldehyde (0.31 g, 10 mmol) and (freshly distilled) n-butanal (0.75 mL, 8.3 mmol). After the mixture was stirred for a further 5 minutes, triethylamine (1 mL, 7.2 mmoles) was added. The mixture rapidly turned purple-brown. After stirring for 30 minutes, the reaction mixture was quenched with glacial acetic acid (5 mL), diluted with 0.05 M HCl (200 mL) and loaded onto a column of Dowex 50W-X2 cation exchange resin. The column was washed with successively with water, 0.5 M HCl and 1M HCl and the adsorbed complexes were removed as a single band with 2 - 4 M HCl. The solution was taken to dryness and dissolved in water (50 mL). $NaHCO_3$ (1.6 g) was added, immediately followed by $NaBH_4$ (0.158 g, 4.2 mmol), dissolved in water (20 mL) containing Na_2CO_3 (2.0 g). The solution was stirred for 30 mins, quenched with 0.5 M HCl (200 mL; caution effervescence), loaded onto a column of Dowex 50W-X2, washed successively with water, 1M HCl then 2M HCl and removed with 4-6 M HCl. The solution was taken to dryness, dissolved in water (250 mL), loaded onto a column of SP-Sephadex C-25 and eluted with Na3Citrate (0.05 M). Two fast-moving purple bands were discarded and the single yellow band was collected, desalted with Dowex/HCl and taken to dryness.
^{13}C N.M.R. δ(75MHz,D_2O): 7.5 ($\underline{C}H_3CH_2$); 27.9 ($CH_3\underline{C}H_2$); 45.8 ($CH_3CH_2\underline{C}_q$); 54.0, 55.3 (NCH_2).

EXAMPLE 3 - *General Diazotisation Procedure for Capping Group Addition*

(a) Preparation of [Co((CH3CH2OCH2CH2O)2-sar)]Cl3 (Compound 1.109), *[Co((HO,CH3CH2OCH2CH2O)-sar)]Cl3 (1.115), [Co((HO)2-sar)]Cl3* (Compound 1.71), *[Co((CH3CH2OCH2CH2O,CH3CH2OCH2CH2OCH2)-absar)]Cl3* (Compound 6.4), *and [Co((HO,CH3CH2OCH2CH2OCH2)-absar)]Cl3* (Compound 6.5)

[Co($(Ham^+)_2$-sar)]$(CF_3SO_3)_5$ (Compound 1.73) (1.12 g, 1 mmol) was dissolved in ethoxyethanol (50 mL). Iso-amyl nitrite (0.34 mL, 2.48 mmol) was added and the solution was

(b) Preparation of [Co((Me,$CH_3CH_2OCH_2CH_2O$)-sar)]Cl_3 (Compound 1.110) *and [Co((Me,$CH_3CH_2OCH_2CH_2OCH_2$)-absar)]Cl_3* (Compound 6.9).

[Co(Me,Ham^+)-sar]$(CF_3SO_3)_4$ (Compound 1.15)(0.50 g, 0.5 mmol) was dissolved in ethoxyethanol (25 mL). Iso-amyl nitrite (0.1 mL, 0.74 mmol) was added and the solution was stirred under nitrogen for 56 hours. Na_2CO_3 (0.040 g) was added, the solution was heated at 65°C for 150 mins, quenched with 4M HCl (25 mL), diluted with water to 200 mL, and loaded onto a column of Dowex 50W-X2. The column was washed successively with water and 1M HCl and the product was eluted with 2-4 M HCl and taken to dryness. The product was dissolved in water (250 mL), loaded onto a column of SP-Sephadex C-25 and eluted with 0.1 M Na3citrate. Two well-separated bands, (B1 orange and B2 yellow) were removed and desalted with Dowex/HCl. The orange band (B1) was loaded onto a column of SP-Sephadex C-25 and elution with 0.1 M K_2SO_4 gave one principal band, followed by a very small diffuse band. These were separately desalted and taken to dryness. The principal band was identified as [Co((Me,$CH_3CH_2OCH_2CH_2O$)-sar)]Cl_3 (Compound 1.110), while the minor product was identified as [Co((Me,HO)-sar)]Cl_3 (Compound 1.10). Chromatography of the yellow fraction (B2) on SP-Sephadex C-25, with 0.1 M K_2SO_4 as eluant gave only one product, which was identified as [Co((Me,$CH_3CH_2OCH_2CH_2OCH_2$)-absar)]Cl_3 (Compound 6.9).

Compound 1.110: ^{13}C N.M.R. δ(75MHz,D_2O): 14.9 ($\underline{C}H_3CH_2O$); 20.2 ($\underline{C}H_3C_q$); 43.1 ($CH_3\underline{C}_q$); 52.7, 55.3, 55.6, 55.7 (NCH_2); 63.4 ($CH_2\underline{C}H_2OC_q$); 67.5 ($CH_3\underline{C}H_2O$); 69.9 ($CH_3CH_2O\underline{C}H_2$); 78.5 ($\underline{C}_qOCH_2$).

Compound 6.9: ^{13}C N.M.R. δ(75MHz,D_2O): 15.1 ($\underline{C}H_3CH_2O$); 20.6 ($\underline{C}H_3C_q$); 43.4 ($CH_3\underline{C}_q$); 45.3, 50.3, 50.7, 52.3, 53.0, 55.4, 58.4, 58.8, 59.3, 60.0, 60.3 (NCH_2); 67.2 ($NC_q\underline{C}H_2$); 67.6 ($CH_3\underline{C}H_2O$); 69.8 ($CH_3CH_2O\underline{C}H_2$); 71.1 ($C_qCH_2O\underline{C}H_2$); 73.6 ($C_qN$).

EXAMPLE 4

Preparation of N-[Co(8-ethylsar-1-yl)]-N'-dimethylaminopropyl-N"-ethylguanidine Trichloride (Compound 1.38)

A solution of myristic acid (0.50g, 2.2mmol) in acetonitrile (5ml) maintained at 50°C was treated with Co(1-amino-8-ethylsar) trichloride (250mg, 0.51mmol), sodium perchlorate

(1.25g) and 1-(3- dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (100mg, 0.52mmol) for 3 days then loaded onto a 7.5cm x 20cm column of Sephadex SP-C25 and eluted with 0.1M aqueous K_2SO_4 solution. The orange eluate is collected and loaded onto a 4cm deep column of Dowex 50W-X4 which is then washed with water and 1M hydrochloric acid. The orange product is removed with 3M hydrochloric acid and the eluate concentrated at ca 5 torr and 30°C to give an orange solid. This is recrystallised (water/acetone) to give N-[Co(8-ethylsar-1-yl)]-N'-dimethylaminopropyl-N"-ethylguanidine trichloride (257mg, 78%) as an orange solid. ^{13}C NMR δ (50MHz, D_2O) 11.3 (CH_3), 18.5 (CH_3), 28.8, 31.2, 40.0, 41.5, 47.2 (CH_3), 50.1, 55.3, 57.3, 59.2, 59.4, 60.6.

EXAMPLE 5 - *Anti-HIV Testing*

The compounds of the invention were tested in a HIV screen by the MTT method (J. Virol. Methods 120: 309-321 [1988]). MT-4 cells (2.5×10^4/well) were challenged with HIV-1 (HTLV-IIIB) or HIV-2 (LAV-2 ROD) at a concentration of 100 CCID50 and incubated in the presence of various concentrations of the test compounds, which were added immediately after challenge with the virus. After 5 days culture at 37°C in a CO_2 incubator, the number of viable cells was assessed by the MTT(tetrazolium) method. Antiviral activity of the compounds is expressed in Table 7 below as ED_{50} (µmol/L). A control test was performed using the known anti-HIV treatment AZT, and a number of comparison compounds were also run through the screen.

stirred under nitrogen for 66 hours. Na_2CO_3 (0.106 g) was added, the solution was refluxed for 150 mins, quenched with 4M HCl (25 mL), diluted with water to 200 mL and loaded onto a column of Dowex 50W-X2. The column was washed successively with water and 1M HCl and the product was eluted with 2-4 M HCl and taken to dryness. The product was dissolved in water (250 mL), loaded onto a column of SP-Sephadex C-25, and eluted with 0.1 M Na3Citrate. Two well-separated bands, (B1 orange and B2 yellow) were removed and desalted with Dowex/HCl. The orange band (B1) was loaded onto a column of SP-Sephadex C-25, and elution with 0.1 M K_2SO_4 gave three bands, which were separately desalted and taken to dryness. The first was the symmetric $[Co((CH_3CH_2OCH_2CH_2O)_2\text{-sar})]Cl_3$ (Compound 1.109), followed by $[Co((HO,CH_3CH_2OCH_2CH_2O)\text{-sar})]Cl_3$ (Compound 1.115), and $Co((HO)_2\text{-sar})]Cl_3$ (Compound 1.71). The yellow band (B2) was similarly chromatographed on SP-Sephadex C-25, using 0.1 M K_2SO_4. In this case one diffuse band was collected in three parts, and each was separately desalted using Dowex/HCl. The leading portion was pure $[Co((CH_3CH_2OCH_2CH_2O,CH_3CH_2OCH_2CH_2OCH_2)\text{-absar})]Cl_3$ (Compound 6.4), while the trailing portion was $[Co((HO,CH_3CH_2OCH_2CH_2OCH_2)\text{-absar})]Cl_3$ (Compound 6.5).

Compound 1.109: ^{13}C N.M.R. δ(75MHz,D_2O): 14.8 ($\underline{C}H_3CH_2O$); 52.6, 55.3 (NCH_2); 63.4 ($CH_2\underline{C}H_2OC_q$); 67.5 ($CH_3\underline{C}H_2O$); 69.8($\underline{C}H_2CH_2OC_q$); 78.5 (C_q).

Compound 1.115: ^{13}C N.M.R. δ(75MHz,D_2O): 15.0 ($\underline{C}H_3CH_2O$); 52.6, 55.1, 55.8, 55.9 (NCH_2); 63.5 ($CH_2\underline{C}H_2OC_q$); 67.6 ($CH_3\underline{C}H_2O$); 69.9($\underline{C}H_2CH_2OC_q$); 73.9 (C_qOH); 78.7; (C_qOCH_2).

Compound 6.4: ^{13}C N.M.R. δ(75MHz,D_2O): 14.9, 15.0 ($\underline{C}H_3CH_2O$); 45.4, 50.4, 50.6, 52.0, 52.7, 53.0, 56.0, 56.4, 58.3, 60.0 (~double intensity) (NCH_2); 63.4 ($CH_2\underline{C}H_2OC_q$); 67.1 ($NC_q\underline{C}H_2$); 67.5 (~double intensity) ($CH_3\underline{C}H_2O$); 69.7, 69.8 ($CH_3CH_2O\underline{C}H_2$); 71.0 ($C_qCH_2O\underline{C}H_2$); 73.6 ($C_qN$); 79.1 ($C_qOCH_2$).

Compound 6.5: ^{13}C N.M.R. δ(75MHz,D_2O): 15.0 ($\underline{C}H_3CH_2O$); 45.4, 50.6, 52.3, 53.0, 53.2, 55.5, 58.3, 58.5, 58.8, 60.1, 60.2 (NCH_2); 67.1 ($NC_q\underline{C}H_2$); 67.5 ($CH_3\underline{C}H_2O$); 69.7 ($CH_3CH_2O\underline{C}H_2$); 71.0 ($C_qCH_2O\underline{C}H_2$); 73.6 ($C_qN$); 74.2 ($C_qOH$).

Table 7

Compound	Counterion	HIV-1 ED_{50} (μmol/L)	HIV-2 ED_{50} (μmol/L)	Hepatitis B ED_{50}(μmol/L)
1.3	Cl	2.6		
1.5	Cl	3.0	1.0	
1.7	CF_3SO_3	1.8		
1.16	Cl	6.2	3.0	
1.17	Cl	13.0	9.8	
1.18	ClO_4	7.0		
1.19	CF_3SO_3	>125		
1.38	Cl	7.6	19	
1.41	Cl	0.53		3
1.44	Cl	1.1		
1.45	CF_3SO_3	1.4		
1.51	Cl			30
1.52	Cl	1.7	5.4	
1.53	Cl			250
1.54	Cl			88
1.65	Cl	12.8		
1.69	Cl	3.9	3.8	
1.72	Cl	7.5		
1.76	Cl	108		
1.88	CF_3SO_3	9.9		
1.114	Cl			50
1.113	Cl			450
1.112	Cl			600
1.115	Cl	4.0	11	
2.14	Cl	4.2		12
2.43	CF_3SO_3	6.6		
5.2	Cl	3.3		
5.5	Cl	0.35		
5.6	Cl	1.2	1.0	

EXAMPLE 6 - *Anti-Duck Hepatitis Testing*

(a) Experimental Animals, Virus and Cell Culture

One day old Pekin-Aylesbury cross-bred ducks congenitally infected with an Australian strain of DHBV (C.J.Freiman and Y.E. Cossart, Australian Journal of Experimental Biology and Medical Science 64 477-484 (1986)) were obtained from a commercial supplier. Ten to fourteen day old ducks were used to obtain primary duck hepatocyte(PDH) cultures. Sera from these animals were tested for DHBV DNA by the dot blot hybridization method (W.S. Mason, M.S. Halpern, J.M. England, G. Seal, J. Egan, L. Coates, C. Aldrich, and J. Summers, Virology 131 373-384 (1983)) and ducklings with an intermediate virus titre [5-10x10^8 viral genome equivalents per ml] were selected for the preparation of congenitally infected primary duck hepatocyte (PDH) cultures. The genome of this strain of DHBV has been molecularly cloned. Hepatocytes were obtained by a modification of the method described by J.S. Tuttleman, J.C. Pugh, and J.Summers Journal of Virology 5B17-25 (1986). Ducks were anaesthetized with ketamine (Parke-Davis, USA) at 30 mg per kg, the liver was surgically removed and perfused with 200 ml of pre-warmed (37°C) Hanks balanced salt solution (calcium and magnesium free) containing 0.5 mM EGTA followed by 200 ml of pre-warmed serum-free Eagle's Essential Medium (MEM) supplemented with 100 mg collagenase type 1 (Boehringer Mannheim, West Germany) and 2.5 mM $CaCl_2$ (Ajax Chemicals, Australia). A single cell suspension was prepared in MEM by gently extruding the perfused liver through a fine wire-gauze mesh. Hepatocytes were purified from the cell mass using Percoll density gradients (Pharmacia, Sweden) following a modification of the manufacturer's specifications. The gradient medium stock solution (SIP; stock isotonic Percoll) consisted of nine parts Percoll mixed with one part 1.5 M NaCl solution. Percoll of the required density of 1.05 g/ml was then generated by diluting six parts SIP with four parts MEM at a final pH of 7.4. Five ml of hepatocyte cell suspension was layered onto 30 ml of this solution and centrifuged at 20,000 rpm for 20 min at 20°C in a JA-20 fixed angle rotor (Beckman, USA). The bands of cells corresponding to the density of hepatocytes (1.07 - 1.09 g/cm^3) were collected and washed in L 15 medium (CSL, Australia) supplemented with 5% fetal bovine serum (FBS) and counted in a haemocytometer. Cell viability was established using trypan blue dye exclusion.

Hepatocytes were diluted and subsequently seeded with L 15 complete (L 15) which consisted of L 15 media supplemented with 15 mM Tris, insulin, glucose, hydrocortisone

hemisuccinate, penicillin and streptomycin according to Tuttleman et al, supra and 5% FBS was also included. Hepatocytes were seeded at approximately 2.0 x 10^6 cells per well into 6 well multiplates (Greiner, West Germany) or at approximately 0.5 x 10^6 cells per well into 24 well plates (Costar, Cambridge Mass.). Hepatocytes were allowed to attach overnight before the first medium change (on day 1post plating) and were maintained with L 15 complete media, at 37°C in a 5% CO_2 humidified incubator, for a total of 10 days The culture medium in both control and treated cultures (see below) was changed every second day.

(b) Preparation of DHBV from Cell Cultures

Total intracellular viral DNA was extracted from cell lysates by a modification of the method of Tuttleman et al, supra. Cells were lysed in a solution containing 0.5% sodium dodecyl sulphate (SDS), 20 mM Tris-HCl (pH 7.4), 10 mM EDTA, 5 mM EGTA, and 150 mM NaCl. DNA was extracted from all samples by digestion with 200 ug per ml of proteinase K (International Biosciences Incorporated, USA) at 37°C for 1 hour, and deproteinised by extraction with an equal volume of phenol:chloroform (1:1), followed by chloroform. The aqueous phase was collected and adjusted to 0.2 M NaCl and the nucleic acids precipitated with 2 volumes of absolute ethanol at -20°C overnight. The pellets were washed in 70% ethanol and then air dried and finally redispersed in TE buffer (10 mM Tris-HCl (pH 8), 1 mM EDTA).

(c) Preparation of radiolabelled DHBV DNA probes

A full length clone of the Australian strain of DHBV was propagated in E. coli and the plasmid extracted using standard techniques (J. Sambrook, E. F. Fritsch and T. Maniatis "Molecular Cloning: A Laboratory Manual" Second Edition Cold Spring Harbour Laboratory Press 1989). The cloned DHBV DNA sequences were excised from the plasmid by EcoRi digestion and were separated by preparative gel electrophoresis using a Prep-A-Gene DNA purification kit (Bio-Rad, Hercules Calif.) according to the manufacturer's recommendations. A 648 bp DNA fragment was also prepared by further digesting the EcoRi DHBV and purifying the smaller fragment as described above. Excised, purified DHBV DNA was radiolabelled with [a-^{32}P] dCTP using a NEN Random Primer Plus Extension kit(NEN Research Products, DuPont, Wilmington, USA) to a specific activity of 0.5-1.0 x 10^9 cpm/mg.

(d) Analysis of DHBV DNA from Hepatocyte Cultures

DHBV DNA in cell culture was detected by slot-blot hybridization. Extracted DNA dissolved in TE buffer was diluted in 6x saline sodium citrate (SSC) 1xSSC is 0.15M NaCl + 0.15M sodium citrate, pH7.0), denatured by rapid boiling and quenching then serially diluted in 6xSSC. A commercial slot-blot apparatus was used to apply the DNA samples to nitrocellulose hybridisation membranes (Hybond C extra, Amersham International, England).

DNA was baked onto membranes at 80°C for 2 hours before pre-hybridisation in a buffer consisting of 50% deionised formamide, 6xSSC, 5mM NaH_2PO_4 (pH 6.5), 2 x Denhardt solution and 100 mg/ml of herring sperm DNA (Boeringer Manheim, Germany). After pre-hybridisation at 42°C for at least 3 hours in a hybridization oven (Hybaid, England) heat-denatured radio-labelled DHBV DNA probe was added to a concentration of at least $2x10^6$cpm and hybridisation allowed to proceed overnight at 42°C. After hybridisation, membranes were washed twice in 2 x SSC-0.1% SDS at 24°C and twice in 0.1 x SSC/0.1% SDS for 30 min at 50°C to remove unbound probe. Radiolabelled DHBV probe bound to the air-dried filters was detected with the aid of intensifying screens by autoradiography at -70°C onto X-OMAT RP film, (Eastman Kodak Co., USA).

(e) Preparation of test compounds

Where possible, stock solutions of test compounds were prepared in sterile deionised distilled water. For compounds with poor aqueous solubility stock solutions were prepared in cell culture grade dimethyl sulphoxide (DMSO). Immediately before each test, dilutions of test compound stock solutions were prepared in deionised distilled water or DMSO at 100x the final test concentration. These dilutions were then added to complete cell culture medium at the rate of 10ml per ml (a dilution of 1 in 100), so that the final concentration of distilled water or DMSO added in every case was constant at 1%, a concentration at which neither DMSO nor distilled water had any effect on virus replication. For tests of antiviral activity, media containing a range of dilutions of test compound were tested against appropriate controls. Negative controls were drug-free media containing only 1% distilled water or DMSO ; positive controls were compounds previously tested and found to have reproducible anti-DHBV activity in this test system.

(f) Assay of viral replication

Following incubation total cellular DNA was extracted as described above (b), and the amount of DHBV DNA detected by slot-blot hybridization and autoradiography as in (d) above.

Areas of hybridization membranes corresponding to each sample were located by alignment with the autoradiographs, cut out and counted for ^{32}P in a gamma radiation counter.

DHBV DNA standards were used to establish both the detection limit, and prove that the relationship between the ^{32}P count and the amount of bound DHBV was linear over the range of interest.

The extent of viral replication (measured as cpm bound ^{32}P bound DHBV probe detected) in the presence of test compounds is expressed as a percentage of viral replication in the control cultures; ED_{50} values were calculated from the dose response curve. The results of the tests are given in Table 7 supra.

EXAMPLE 7 - *Mouse test for Mammalian Toxicity*

All tests were carried out on fully-grown Male white mice (*Mus musculus*) strain BALB/c weighing 20 to 25g per mouse, supplied by the Animal Breeding Unit of the University of N.S.W. The mice were obtained at least one day prior to the test day and acclimatised in the test room (Temp 25°C), where they were held, five to a box and given commercial rat pellets and water *ad lib.*

On the day of the test, the compound to be tested was weighed out and dissolved in either olive oil or DMSO to give a stock solution which when injected at the rate of 100 ml per mouse gave a dose of 100 mg/kg. Two further doses of 10 mg/kg and 1.0 mg/kg were prepared from this solution.

100 ml of a solution was injected intraperitoneally into each test mouse. Five or ten mice were dosed at each concentration i.e. 100mg/kg, 50 mg/kg, 10mg/kg and 1mg/kg, with five control mice dosed with solvent.

In the case of those compounds tested for multiple dosing, the injections were repeated, as above, each day at the same time of day, for the number of days required.
The mice were observed at half-hourly intervals and symptoms recorded. Further readings were taken for the next seven days. The results after 7 days are shown in Table 8 below.

Table 8

Compound Number	No. mice dead/No. mice injected at dose			
	100mg/kg	50mg/kg	10mg/kg	1mg/kg
1.52 *	0/10	0/10	0/10	-
1.73	0/5	0/5	-	-
1.71	5/5	0/5	-	-
1.57	5/5	-	0/5	0/5
5.5 *	0/5	0/5	0/5	-

* Five mice were given repeated injections of compound at a dose of 100mg/kg daily for 5 successive days without ill effects.

EXAMPLE 8 - *Anti Human Hepatitis Testing*

Tests of antiviral activity in human cells infected with Hepatitis B were performed according to the method of Korba and Gerin reported in Antiviral Research, **19**, 55-70 (1992) and the results are shown in Table 9.

Table 9

Compound No.	IC_{50} (μm/L)	AI_{50}	IC_{90} (μm/L)	AI_{90}
1.52	0.11	1300	0.81	180
1.73 (diprotonated)	1.6	773	13	95

EXAMPLE 9

The following formulation A may be prepared by wet granulation of the ingredients with a solution of povidone, followed by addition of magnesium stearate and compression.

		mg/tablet	
Formulation A			
(a)	Active ingredient	250	250
(b)	Lactose B.P.	210	26
(c)	Povidone B.P.	15	9
(d)	Sodium starch glycollate	20	12
(e)	Magnesium stearate	5	3
		500	300

The following formulation B, may be prepared by direct compression of the admixed ingredients.

Formulation B	mg/capsule
Active ingredient	250
Pregelatinised starch NF15	150
	400

Formulation C (Controlled release formulation)

This formulation may be prepared by wet granulation of the ingredients (below) with a solution of povidone followed by the addition of magnesium stearate and compression.

		mg/tablet
(a)	Active ingredient	500
(b)	Hydroxypropylmethylcellulose (methocel K4M Premium)	112
(c)	Lactose B.P.	53
(d)	Povidone B.P.C.	28
(e)	Magnesium stearate	7
		700

EXAMPLE 10- *Capsule Formulations*

Formulation A

A capsule formulation may be prepared by admixing the ingredients of Formulation B in Example 9 above and filling into a two-part hard gelatin capsule. Formulation B (infra) may be prepared in a similar manner.

Formulation B

		mg/capsule
(a)	Active ingredient	250
(b)	Lactose B.P.	143
(c)	Sodium starch glycollate	25
(d)	Magnesium stearate	2
		420

Formulation C (Controlled release capsule)

The following controlled release capsule formulation may be prepared by extruding ingredients a, b and c using an extruder, followed by spheronisation of the extrudate and drying. The dried pellets may then be coated with release-controlling membrane (d) and filled into a two-piece, hard gelatin capsule.

		mg/capsule
(a)	Active ingredient	250
(b)	Microcrystalline cellulose	125
(c)	Lactose B.P.	125
(d)	Ethyl cellulose	13
		513

EXAMPLE 11 - *Injectable Formulation*

Formulation:

Active ingredient	0.200 g
Hydrochloric acid solution, 0.1M	qs to pH 5.0-7.0
Sodium hydroxide solution, 0.1M	qs to pH 5.0-7.0
Sterile water	qs to 10 ml

The active ingredient may be dissolved in most of the water (35°-40°C) and the pH adjusted to between 5.0 and 7.0 with the hydrochloric acid or the sodium hydroxide as appropriate. The batch may then be made up to volume with the water and filtered through a sterile micropore filter into a sterile 10 ml amber glass vial (type 1) and sealed with sterile closures and overseals.

EXAMPLE 12 - *Antiviral Activity*

The compounds of the present invention were tested for their ability to inhibit RNA synthesis in an *in vitro* polymerase assay (Chu and Westaway, 1985, 1987; Brun and Brinton, 1986). In this assay, flavivirus RNA comprising the genomic 44S RNA, a double-stranded replicative form (RF) and a partially-double-stranded replicative intermediate (RI) was detected by the incorporation of [a-^{32}P]GTP.

(a) Preparation of virus-infected Vero cell extracts

Vero cells were infected at a multiplicity of infection of 7 for Type 2 dengue (DEN-2) virus (New Guinea C strain; Sabin and Schlesinger, 1945) of Kunjin (KUN) virus (strain MRM 61C; Boulton and Westaway, 1972). Extracts containing RNA-dependent RNA polymerase (RDRP) activity derived from DEN-2 virus-infected cells were prepared at 30 to 36 h p.i., when polymerase activity was at a maximum. Similarly, extracts of KUN virus-infected cells were prepared at the time of maximum polymerase activity at 24 h p.i. (Chu and Westaway, 1985).

The cells were pelleted by centrifugation and resuspended in 10 mM sodium acetate at a concentration of $2x10^7$ cells/ml. They were then disrupted by passaging 20 times through a 21 gauge needle followed by 20 times through a 26 gauge needle. The disrupted cells were centrifuged at 800 g for 7 min to obtain a supernatant fraction and a pellet of the nuclear-associated material. All RDRP assays were performed using the supernatant fraction, hereafter referred to as the cell extract, which was stored at -70°C and used after only one cycle of freeze/thawing.

(b) RNA-dependent RNA polymerase assay

The RDRP activity in the cell extract was assayed as previously described with the following modifications (Chu and Westaway, 1985). In each RDRP assay the virus-infected cell extract contained 4.5-6 mg/ml of protein. The compound to be tested dissolved in double distilled water and RNasin (0.5 unis/ml, Promaga) were added to the cell extract for 10 min prior to the addition of the other components of the RDRP assay. The final reaction mixture (total volume of 50 ml) contained 50 mM Tris-HCl pH 8.0, 10 mM magnesium acetate, 7.5 mM potassium acetate, 10 mM 2-mercaptoethanol, 6 mg actinomycin D (AMD), 5 mM phosphoenolpyruvate, 3 units/ml pyruvate kinase, 0.5 mM ATP, 0.5 mM CTP, 0.5 mM UTP, 25 mM GTP, 5 mCi [a-^{32}P]GTP (Amersham, specific activity 410 Ci/mmol), 0.5 units/ml RNasin, 30 ml of infected cell extract and the test compound (from 0.5 to 100 mM). The reaction was stopped after 30 min at 37°C by the addition of EDTA to a final concentration of 10 mM. An equal volume of TNE-SDS (50 mM Tris-acetate pH 7.6, 0.1 M sodium acetate, 1 mM EDTA and 2% SDS) was added to disrupt membranes. The RNA was then extracted with phenol and precipitated by ethanol.

C. Electrophoresis of RNA

RNA samples were mixed with an equal volume of sample buffer containing 7 M urea in TBE (89 mM Tris-HCl, 89 mM boric acid, 2.5 mM EDTA) and 0.5% bromophenol blue, and were separated by electrophoresis through 3% polyacrylamide gels containing 7 M urea in TBE. The gels were fixed in 10% acetic acid, dried and radiolabelled bands detected by autoradiography.

Results

The compounds tested inhibited the synthesis of both DEN-2 and KUN RF RNA. There was also a decrease in the amount of RI detected with increasing concentration of drug. The concentrations which give > 75% inhibition of RNA synthesis are given in Table 10.

Table 10

Compound	Counterion	ED_{50} (μmol/L)
1.17	Cl	25
1.23	Cl	40
1.41	Cl	<2.5
1.42	Cl	<12.5
1.44	Cl	<12.5
1.69	Cl	50
1.71	Cl	60
2.14	Cl	30
3.8	Cl	<12.5
5.6	Cl	3.5
5.6	ClO_4	2.5

References:

BOULTON, R.W. AND WESTAWAY, E.G. (1972).

Comparisons of Togaviruses:Sindbis virus (Group A) and Kunjin virus (Group B). *Vitrology* 49, 283-289.

CHU, P.W.G. AND WESTAWAY, E.G. (1985).

Replication strategy of Kunjin virus:evidence for recycling, role of the replicative form RNA as template in semiconservative and asymmetric replication. *Virology* 140, 68-79.

CHU, P.W.G. AND WESTAWAY, E.G. (1987)

Characterisation of Kunjin virus RNA-dependent RNA polymerase:reinitiation of synthesis in vitor. *Virology* 157, 330-337.

GRUN, J.B. AND BRINTON, M.A. (1986)

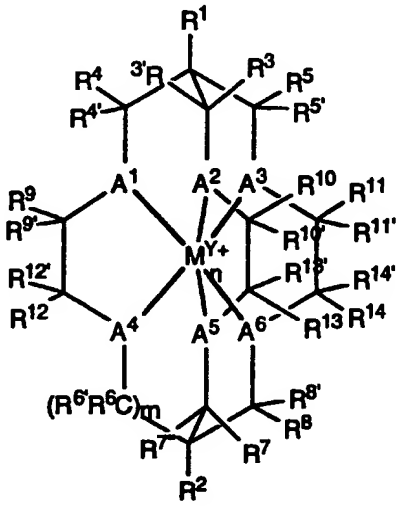
Characterisation of West Nile virus RNA-dependent RNA polymerase and cellular adenylyl and uridylyl transferases in cell-free extracts. *Journal of Virology* 60, 1113-1124.

SABIN, A.B. AND SCHLESINGER, R.W. (1945).

Production of immunity to dengue with virus modified by propagation in mice. *Science* 101, 640-642.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for the treatment and/or prophylaxis of a viral infection which comprises administration of an effective amount of a compound of Formula 1:



Formula 1

wherein

M is a metal capable of forming hexacoordinate complexes;

Y is an integer between 1 and 6;

n is 0 or 1;

m is 0 or 1;

A^1 to A^6 inclusive are metal coordinating groups which may be the same or different and are selected from NH, N, O and S;

R^1 and R^2 may be the same or different and are selected from hydrogen, halogen, nitro, cyano, optionally substituted alkyl, optionally substituted alkylene, optionally substituted aryl, hydroxy, optionally substituted alkoxy, optionally substituted alkyenyloxy, optionally substituted alkynyloxy, optionally substituted aryloxy, optionally substituted acyloxy, optionally substituted amino, optionally substituted ammonium, optionally substituted cycloalkyl, optionally substituted acyl, optionally substituted saturated or unsaturated heterocyclyl, optionally substituted heteroaryl, carbamato, thiocarboxylato, amidino,

alkoxycarbonyl, mercaptothiocarbonyl, alkoxythiocarbonyl, thiocarbamato, zinc halide and a sugar moiety; and

R^3 to R^{14} and $R^{3'}$ to $R^{14'}$ inclusive may be the same or different and are selected from hydrogen, halogen, optionally substituted alkyl, optionally substituted alkylene, hydroxy, optionally substituted alkoxy, optionally substituted alkyenyloxy, optionally substituted alkynyloxy, optionally substituted aryloxy, optionally substituted acyloxy, optionally substituted amino, optionally substituted ammonium, optionally substituted cycloalkyl, optionally substituted acyl, optionally substituted aryl, optionally substituted saturated or unsaturated heterocyclyl, optionally substituted heteroaryl, carbamato, thiocarboxylato, amidino, alkoxycarbonyl, mercaptothiocarbonyl, alkoxythiocarbonyl, thiocarbamato and a sugar moiety; or

one or more of the groups A^1 to A^6 may be linked to an adjoining carbon atom by a double bond with the absence of the corresponding R^3 to R^{14} and $R^{3'}$ to $R^{14'}$ group,

salts thereof, pharmaceutically acceptable derivatives thereof, pro-drugs thereof, tautomers thereof and/or isomers thereof to a subject requiring said treatment and/or prophylaxis.

2. A method according to Claim 1, wherein M is an alkali metal, alkaline earth metal or a transition metal.

3. A method according to Claim 2, wherein the alkali earth metal is lithium or sodium.

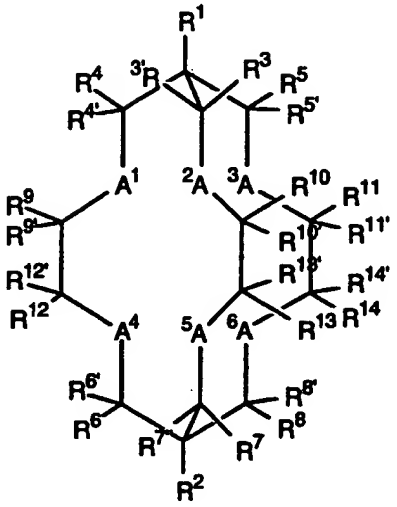
4. A method according to Claim 2, wherein the alkaline earth metal is magnesium.

5. A method according to Claim 2, wherein the transition metal is vanadium, titanium, chromium, manganese, iron, cobalt, nickel, copper, zinc, ruthenium, silver, cadmium, iridium, platinum, indium or mercury.

6. A method according to Claim 2 or Claim 5, wherein the transition metal is a Group 9 metal.

7. A method according to Claim 6, wherein the Group 9 metal is cobalt.

8. A method according to Claim 1, wherein the compound of Formula 1 has the Formula 2:



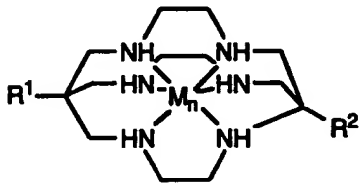
Formula 2

wherein

A^1 to A^6, R^1 to R^{14} and $R^{3'}$ to $R^{14'}$ are as defined in Claim 1.

9. A method according to any one of the preceding claims, wherein A^1 to A^6 inclusive are NH, N or S.

10. A method according to any one of Claims 5 to 7 and 9, wherein the compound of Formula 1 has the Formula 3:



Formula 3

wherein

R^1, R^2, M and n are as defined in Claim 1.

11. A method according to any one of the preceding claims, wherein R_1 and R_2 are hydrogen, halogen, nitro, cyano, optionally substituted alkyl, optionally substituted aryl,

hydroxy, optionally substituted alkoxy, optionally substituted acyloxy, optionally substituted amino, optionally substituted ammonium, optionally substituted acyl or optionally substituted saturated or unsaturated heterocyclyl.

12. A method according to any one of the preceding claims, wherein R_1 and R_2 are lower alkyl.

13. A method according to Claim 12, wherein the lower alkyl is ethyl.

14. A method according any one of the preceding claims, wherein R^3 to R^{14} and $R^{3'}$ to $R^{14'}$ are hydrogen or optionally substituted alkyl.

15. A method according any one of the preceding claims, wherein the viral infection is caused by a Retrovirus, Herpesvirus, Hepadnavirus or Flavivirus.

16. A method according to any one of the preceding claims, wherein the viral infection is AIDS, Adult T-cell leukemia, cold sores, genital herpes, CMV, cytomegalic inclusion disease, chicken pox, shingles, infectious mononucleosis, Hepatitis B, Hepatitis C, non-A non-B Hepatitis, canine arthritis/encephalitis, feline arthritis, duck hepatitis, dengue fever, yellow fever or Japanese encephalitis.

17. A method according to any one of the preceding claims, wherein the compound of Formula 1, 2 or 3 is administered in the form of two or more sub-doses per day.

18. A method according to Claim 17, wherein the sub-doses are administered in unit dosage forms.

19. Use of a compound of Formula 1, 2 or 3 as defined in any one of Claims 1 to 14 in the manufacture of a medicament for the treatment and/or prophylaxis of a viral infection.

20. A compound of Formula 1, 2 or 3 as defined in any one of Claims 1 to 14 for use in the treatment and/or prophylaxis of a viral infection.

21. A pharmaceutical or veterinary composition for the treatment and/or prophylaxis of a viral infection which comprises a compound of Formula 1, 2 or 3 as defined in any one of Claims 1 to 14 in association with a pharmaceutically or veterinarily acceptable carrier, diluent, adjuvant and/or excipient.

22. A process for the preparation of a compound of Formula 1 as defined in any one of Claims 1 to 14 wherein n is 1 and A^1 to A^6 inclusive are N or NH which comprises the steps of:

(a) reacting a metal complex having at least three terminal primary amino groups with formaldehyde, a base and a nucleophile optionally containing a functional group which may react with any co-ordinated amine which may also be present on the metal complex leading to encapsulation and the formation of a cage molecule; and

(b) optionally modifying the cage molecule.

23. A compound of Formula 1 or 3 as defined in any one of Claims 1 to 7 and 9 to 14 which is Compound No. 1.3, 1.14, 1.16, 1.18, 1.20, 1.23, 1.24, 1.26, 1.28-1.45, 1.47-1.49, 1.51-1.56, 1.58, 1.60-1.62, 1.64, 1.81-1.87, 1.95-1.97 or 1.103-1.117 in Table 1, Compound No. 3.15 or 3.16 in Table 3, Compound No. 4.1-4.5 in Figure 1, Compound No. 5.2-5.12 in Table 4, Compound No. 6.1-6.9 in Table 5 or Compound No. 7.1-7.5 in Table 6.

24. A method for the treatment and/or prophylaxis of a viral infection which comprises administration of an effective amount of a compound of Formula 1 or 3 as defined in Claim 23 to a subject requiring said treatment and/or prophylaxis.

25. A method according to Claim 24, wherein the viral infection is caused by a Retrovirus, Herpesvirus, Hepadnavirus or Flavivirus.

26. A method according to Claim 24 or Claim 25, wherein the viral infection is AIDS, Adult T-cell leukemia, cold sores, genital herpes, CMV, cytomegalic inclusion disease, chicken pox, shingles, infectious mononucleosis, Hepatitis B, Hepatitis C, non-A non-B Hepatitis, canine arthritis/encephalitis, feline arthritis, duck hepatitis, dengue fever, yellow fever or Japanese encephalitis.

27. A method according to any one of Claims 24 to 26, wherein the compound of Formula 1 or 3 is administered in the form of two or more sub-doses per day.

28. A method according to Claim 27, wherein the sub-doses are administered in unit dosage forms.

29. Use of a compound of Formula 1 or 3 as defined in Claim 23 in the manufacture of a medicament for the treatment and/or prophylaxis of a viral infection.

30. A compound of Formula 1 or 3 as defined in Claim 23 for use in the treatment and/or prophylaxis of a viral infection.

31. A compound of Formula 1 or 3 as defined in Claim 23 for use in therapy.

32. A pharmaceutical or veterinary composition for the treatment and/or prophylaxis of a viral infection which comprises a compound of Formula 1 or 3 as defined in Claim 23 in association with a pharmaceutically or veterinarily acceptable carrier, diluent, adjuvant and/or excipient.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 95/00283

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61K 31/555; C07D 487/08, 495/08, 513/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC A61K 31/555, C07D 487/08, 495/08, 513/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU : IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DERWENT
CAS ONLINE : substructure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AU,A, 54235/90 (SALUTAR INC) 18 October 1990 see page 17 lines 4-7, page 28 lines 25 to page 30 line 24 and claim 32	21
X	Nuclear Medicine and Biology - International Journal of Radiation Applications and Instrumentation, vol. 18, no. 8 (1991), pages 855-858 see whole document especially page 857 column 2 and page 858 column 1	21

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 1995	29 AUGUST 1995
Name and mailing address of the ISA/AU AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (06) 285 3929	Authorized officer O.L. CHAI Telephone No.: (06) 283 2484

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	Chemical Abstracts, vol. 118, abstract no. 138517, Geue, Rodney J et al, "Metal ion cages : capping reactions with bifunctional methylene compounds and formaldehyde" (& Aust. J. Chem (1992), 45(10), pages 1681-703)	22 23
A	Chemical Abstracts, vol 102, abstract no 16421, Geue, Rodney J et al, "Synthesis, chiroptical properties, and electron self-exchange reactivity of a rigid pentacyclic metal ion cage system with D3 symmetry" (& J. Am. Chem. Soc. (1984), 106(26), pages 8282-91)	22,23
A	Chemical Abstracts, vol. 107, abstract no. 108126, Bull, Daryl J et al, "Synthesis and characterization of encapsulated cobalt (III) hydroxylamine complexes" (& Inorg. Chem. (1987), 26(18), pages 3040-3)	23
A	Chemical Abstracts, vol 112, abstract no 190689, Gahan, Lawrence R et al, "Synthesis, x-ray crystal structure, and metal ion extraction from a nitrogen-sulfur "pendant arm" encapsulated complex of cobalt (III)" (& Inorg. Chem. (1990), 29(7), pages 1451-4)	23
A	Chemical Abstracts, vol 114, abstract no 134863, Hohn, Arthur, "A new strategy for the metal template synthesis of organic metal ion cages (& J. Chem. Soc., Chem Commun. (1990), (21), pages 1473-5)	23
A	Chemical Abstracts, vol 119, abstract no 240294, Lay, Peter A et al, "The Synthesis and properties of cobalt cage complexes with nitrogen-sulfur (N_3S_3) donor sets", (& Aust. J. Chem. (1993), 46(5), pages 641-661)	23
A	Chemical Abstract, vol 121, abstract no 49002, Creaser, Inge, I et al, "New macrocyclic complex is derived from cobalt (III) cage complexes", (& Aust. J. Chem. (1994), 47(3), pages 529-44)	23

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No.
PCT/AU 95/00283

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
AU	54235/90	US	5364613	CA	2051648	EP	474642
		EP	481526	FI	914714	HU	60277
		JP	4504436	NO	913920	WO	9012050

END OF ANNEX